Lacosamide for neuropathic pain associated with diabetic peripheral neuropathy

**Summary**

**Clinical and Patient Impact**

- Lacosamide is an anticonvulsant that is being investigated for the treatment of epilepsy and neuropathic pain. The precise mechanism by which lacosamide exerts its analgesic effects is not clear, although it is claimed to be unrelated to the mechanisms of currently available drugs. An application for marketing authorisation was submitted to the EMEA, in August 2007, for the proposed indication of the treatment of neuropathic pain associated with diabetic peripheral neuropathy in adults.

- Fully published data are only available from one phase II study. Phase III data from five studies (including one open-label study and two open-label extension studies) are only available in the form of conference posters. In the three short-term placebo-controlled studies, lacosamide produced a reduction in the 11-point Likert pain scale of approximately 1.9 to 3.1 points at study end. However, not all results were statistically significant and placebo-subtracted reductions were approximately 0.3 to 0.9 points. A reduction of two points on an 11-point Likert pain scale is classed as being clinically significant.

- Analgesia in painful diabetic neuropathy is very seldom totally effective. Consequently, the impact of pain-relief on patient function, such as work, social activities and other quality of life measures, is important in assessing response. More data are required for lacosamide in order to determine any benefits in these areas.

- In phase III studies, treatment discontinuation was high, with one 18-week study reporting discontinuation rates of 66% and 43% for lacosamide 600mg/day and 400mg/day, respectively, vs. 32% for placebo. 42% of withdrawals from the 600mg/day arm were attributed to adverse events, with CNS effects such as blurred vision, nausea, dizziness, tremor, somnolence, and balance disorder possibly being dose-related.

**NHS and Financial Impact**

- The company anticipate that lacosamide will be used in patients either not responding to, or not tolerating existing treatments, or where existing treatments are contraindicated. The manufacturer anticipates that lacosamide will be similarly priced to pregabalin*, and have estimated that it will cost the NHS approximately £3.6 million in 2008, rising to £27.8 million by 2011. Many existing therapies are available as generics and the prescribing of a more expensive branded product in preference to these would lead to an increase in expenditure. Currently available efficacy and safety data for lacosamide do not support such a shift in prescribing.
### Introduction

Diabetic neuropathy is a common, incurable complication of diabetes. It can be classified as peripheral, autonomic, proximal or focal, although more than one type may develop in the same patient [1, 2]. Peripheral (distal) neuropathy is the most common type and patients with progressive nerve damage can develop symptoms and signs that include numbness, loss of temperature sensation, tingling, burning, hypersensitivity to touch, and pain (although some patients are asymptomatic) [1]. Symptoms typically develop in a glove and stocking pattern of sensory loss, potentially leading to chronic painful diabetic peripheral neuropathy (PDPN) [3].

Neuropathies can develop at any time, although the risk increases with the duration of diabetes, and the highest rates are seen in individuals who have had diabetes for at least 25 years [1]. The exact mechanism behind the nerve damage is uncertain, but it is thought to involve a combination of factors, including metabolic (e.g. poor glycaemic control and hyperlipidaemia), neurovascular, autoimmune, and lifestyle (e.g. smoking or alcohol use) [1]. Intensive glycaemic control has been shown to slow its progression in patients with insulin-dependent diabetes [2].

Two recent, UK community-based studies (involving mainly people with type 2 diabetes) have reported PDPN to affect around 16–26% of people with diabetes, with many experiencing chronic moderate or severe pain that was frequently unreported, inadequately treated and reduced quality of life [4,5]. No international consensus exists about treatment choices for PDPN, but a recent systematic review has concluded that antidepressants and anticonvulsants, many of which are not specifically licensed for this indication, are still the most commonly used options in its management [6]. Tricyclic antidepressants (TCAs) and traditional anticonvulsants were found to be better for short-term pain relief than the newer generation anticonvulsants, but long-term efficacy data is lacking for all classes of agent. The review also highlighted the limited efficacy of current pharmacological treatment, with three patients needing treatment with amitriptyline (one of the most efficacious drugs), for one patient to achieve the endpoint of a 50% reduction in pain score [7]. As many patients do not achieve more than 30–50% pain reduction [8], measures of function, such as work and social activities, and quality of life, are also important in assessing response.

### Drug action

Lacosamide is an anticonvulsant that is being investigated for the treatment of epilepsy and neuropathic pain. The precise mechanism by which lacosamide exerts its analgesic effects is not clear, although it is claimed to be unrelated to the mechanisms of currently available drugs [Personal Communication, UCB Pharma, July 2007]. Healthy volunteer studies show that oral lacosamide is rapidly and almost completely absorbed, with a maximum plasma concentration reached approximately one to four hours after dosing [9]. The plasma elimination half-life is approximately 13 hours, and steady state is achieved within three days of repeated oral administration. Data suggest a low intra- and inter-subject variability, and food does not affect the drug’s pharmacokinetic parameters.

Lacosamide has no effect on the pharmacokinetics of carbamazepine, valproic acid, metformin, digoxin, or oral contraceptives [Personal Communication, UCB Pharma, July 2007].

### Proposed indication and marketing

The proposed indication for lacosamide is for the treatment of neuropathic pain associated with diabetic peripheral neuropathy in adults. An application for marketing authorisation was submitted to the EMEA in August 2007, and the manufacturer intends to market the drug under the brand name Vimpat® [Personal Communication, UCB Pharma, July/August 2007].

### Proposed cost/course

Lacosamide will be available as tablets (strengths to be confirmed) to be administered in two equally divided daily doses. The proposed recommended starting dose is 100mg/day, increasing to an initial therapeutic dose of 200mg/day after one week. Based on individual patient response and tolerability, the dose can be further increased by 100mg/day every week, to a maximum recommended dose of 600mg/day. The NHS price of lacosamide has yet to be agreed with the Department of Health; however, the manufacturer anticipates that the price will be similar to pregabalin (Lyrica®) [Personal Communication, UCB Pharma, July 2007].

### Efficacy

Fully published data are only available from one phase II study [10]. Phase III data from five studies (including one open-label study
Patients enrolled in the placebo-controlled studies had a diagnosis of type 1 or 2 diabetes and a history of neuropathic pain for up to five years duration, with average daily pain scores of ≥4 on the 11-point Likert scale (0 = no pain, 10 = worst possible pain). After a run-in phase to wash out prohibited medications (four weeks in the phase II study, two weeks in the phase III studies), eligible patients were randomised to placebo or lacosamide groups and then entered a six-week titration phase during which daily doses were up-titrated weekly using 100mg increments and sham doses as appropriate [Personal Communication, UCB Pharma, July/August 2007]. This was followed by a maintenance phase (four weeks in the phase II study, 12 weeks in the phase III studies) after which patients underwent a one-week dose-taper phase and two-week safety follow-up, or entered a two-week transition phase for entry into an open-label extension study (phase III trial participants only). The primary endpoint appears to vary slightly between the trials, but involved the change from baseline in the self-reported daily 11-point Likert pain scores. Secondary endpoints assessed pain intensity and overall pain, sleep, activity, mood, and quality of life (QoL) measured with the SF-36 instrument [10, 14, 15].

Phase II data
A multicentre, double-blind dose escalation study (n=119) assessed the efficacy of lacosamide vs. placebo in patients with PDPN [10]. Eligible patients were 18 years or older with a glycosylated haemoglobin (HbA₁c) of ≤10% for at least three months prior to the study. Exclusion criteria included clinically important ECG abnormalities, creatinine clearance <60mL/min, and raised liver enzymes. The concomitant use of certain medications was not allowed e.g. anticoagulants, anticonvulsants, tricyclic antidepressants, benzodiazepines, and other painkillers (except paracetamol at a maximum dose of 2g/day as analgesic rescue medication).

Patients were randomised to placebo or lacosamide titrated up to a maximum of 400mg/day. The highest attained tolerated dose from the titration phase was maintained for the ensuing four-week maintenance period, after which all trial medication was stopped at the end of the taper period. The primary outcome measure was the change in self-recorded, daily 11-point Likert pain scores from baseline to the end of the maintenance phase in the intention-to-treat, last observation carried forward (LOCF) population. This form of data analysis assumes that the last result, observed before a subject drops out of a trial, would have occurred at that level if the patient had remained until the end of the trial. It is used when data are missing due to loss to follow-up and can lead to biased treatment estimates.

Phase III placebo-controlled trial data
In a European multicentre, double-blind, placebo-controlled study (n=357), patients who still met the eligibility criteria after the run-in phase were randomised 1:2:2 to receive placebo, lacosamide 400 mg/day, or 600mg/day, administered in two equally divided doses, during the 12-week maintenance phase [14] (poster). The primary endpoint was stated to be the change in daily pain score from baseline using an 11-point Likert scale, but the time point at which this change was to be measured in the study is not stated. 246 patients (70%) completed the study (80%, 75%, and 56% in the placebo, 400mg/day and 600mg/day groups, respectively) [14].

Pain scores progressively decreased over the treatment period in all groups, with reductions in Likert pain scores reported to be statistically significantly superior for lacosamide 600mg/day vs. placebo (P-values ranged from 0.0011 to 0.0344) at each visit, except the last visit (week 18). Statistically significant differences between the 400mg/day group and placebo were seen between week 5 and week 14 (P-values ranged from 0.0045 to 0.0234). No absolute data were provided, but the available graphical data suggest that at week 18 (last visit) both lacosamide groups achieved a reduction in Likert pain scores of approximately 2.0 points, compared to approximately 1.6 for placebo (i.e. a difference of approximately 0.4 points). Analysis of the mean daily Likert pain score at the last four weeks of the 12-week maintenance phase showed reductions of 1.90 and 1.86 for the 400mg/day and 600mg/day lacosamide treatment groups.

23% of lacosamide and 19% of placebo recipients did not complete the trial, with lack of efficacy, adverse events and withdrawal of consent the most commonly cited reasons for withdrawal. Baseline Likert pain scores were 6.5–6.6 and scores progressively decreased over the study in both lacosamide and placebo recipients. Least square mean reductions from baseline to the end of the maintenance period were 3.11 for lacosamide recipients, and 2.21 for those receiving placebo (treatment difference 0.9, 95% CI 0.0–1.8; P=0.039). The percentage of patients achieving at least a two-point reduction in the Likert pain score (predefined as indicative of clinical significance) was 60% in the lacosamide arm and 51% in the placebo arm [10]. This suggests that around 11 patients needed to be treated with lacosamide instead of placebo for one patient to achieve a clinically significant reduction in their Likert pain score in this trial.

Statistically significant differences in favour of lacosamide were seen in secondary outcome measures such as sleep, general activity, pain intensity, and overall pain, although the clinical significance of these mean changes is unclear. The percentage of pain-free days (Likert pain score of 0) was 18% for lacosamide recipients vs. 8% for placebo. In terms of QoL, statistical significance was only reported for two out of the eight domains measured using the SF-36 (bodily pain and vitality). No absolute data were provided so the clinical significance of any differences cannot be assessed. Mood assessments showed no statistically significant differences vs. placebo [10].
Lacosamide

respectively, compared with baseline. These reductions were not statistically significantly different compared to placebo (no further data provided) [14].

Both lacosamide groups showed statistically significant improvements over placebo for the perception of pain interference with sleep and general activity. Improvements (mildly, moderately, or much better) in the patients' global impression of change in pain from baseline to the end of the treatment were seen for 79% of patients in the 400 mg/day group compared to 62% in the placebo group (P<0.05), and 74% in the 600mg/day group. It is reported that improvements in the SF-36 QoL scores were seen in all treatment arms and both lacosamide treatment groups showed a greater improvement in the ‘physical functioning’ and ‘general health’ components, and in the overall physical component summary compared with placebo [14]. However, no data are provided so the clinical significance of any reported differences cannot be assessed.

In a US multicentre, double-blind, placebo-controlled study (n=469), patients who still met the eligibility criteria after the run-in phase were randomised 1:2:2:2 to receive placebo, 200mg/day, 400mg/day or 600mg/day lacosamide during the 12-week maintenance phase, administered in two equally divided doses [15] (poster). Of the 468 patients who were randomised and received at least one dose of lacosamide, only 55% completed the study (68%, 67%, 57%, and 34% from the placebo, 200mg/day, 400mg/day, and 600mg/day lacosamide groups, respectively).

The mean reduction of the Likert pain score from baseline to the last four weeks of the maintenance phase (the primary endpoint) was 2.2 in the 200mg/day group, 2.5 in the 400mg/day group, and 2.4 in the 600mg/day group, compared with 1.8 in the placebo group. Using a conventional P-value of 0.05 as the threshold for statistical significance, there was no significant difference between any of the lacosamide groups and placebo for this primary endpoint. (However, the authors claim that the 400mg/day lacosamide group was statistically superior to placebo, quoting a P-value of 0.0507). When Likert pain scores were analysed weekly (a secondary variable), statistically significant differences were reported to be seen between the lacosamide 600mg/day and placebo groups from as early as week 2 through until week 18. However, lacosamide showed no statistically significant differences over placebo in changes from baseline to the last four weeks of the maintenance phase in any of the other secondary efficacy variables [15].

Phase III open-label study data

All the open-label studies are ongoing and results presented below are from interim analyses. Patients received lacosamide titrated to their optimal dose (up to 600mg/day) in weekly increments of 100mg/day, before they entered a long-term maintenance period. Dose adjustments were allowed as necessary and the most frequently taken dose was 400mg/day. Efficacy was measured using within-subject change in average daily pain score using an 11-point Likert scale and other measures included assessments of overall pain using the Visual Analog Scale (VAS), pain interference with sleep and general activity, Patient’s Global Impression of Change in Pain (PGIC) and QoL [11–13].

214 subjects who had completed the European phase III placebo-controlled trial directly enrolled in an open-label, follow-on trial to assess the long-term efficacy and safety of lacosamide [12] (poster). The median duration of lacosamide exposure was 358 days, and the maximum duration was 591 days. At the cut-off date 26% of patients had withdrawn from the study. The average daily pain score on the Likert pain scale was 6.6 at the baseline of the original double-blind study and this was reduced by 3.3 points over the entire treatment period (double-blind and open-label extension phases). Improvements in assessment of overall pain, and pain interference with sleep and general activity were of a similar magnitude [12].

451 subjects who were previously enrolled in one of two double-blind trials (93%) or an open-label trial (7%) of lacosamide entered a US multicentre, open-label, follow-on study [13] (poster). The mean duration of treatment was 216 days (up to a maximum of 516 days). At the cut-off date 30% of patients had withdrawn from the study. The main reasons for treatment discontinuation included adverse events (12%) and withdrawal of consent (9%). Lack of efficacy led to withdrawal of 3% of subjects [13]. The reductions in average daily pain score achieved in the original trials were reported to have further increased during open-label treatment. The mean reduction from baseline to the entire titration phase, entire maintenance phase, and entire treatment phase was 3.1, 3.8, and 3.5 points on the Likert scale, respectively. The percentage of patients reporting feeling “better” (comprising much better, moderately better, or mildly better) using the PGIC ranged from 94% to 98% [13]. The PGIC was assessed at six months into the maintenance phase and at each subsequent clinic visit.

In a European multicentre, open-label, long-term trial (n=371), patients who still met the eligibility criteria after a two-week run-in phase were titrated to their optimal lacosamide dose [11] (poster). The median duration of treatment was 211 days (maximum of 385 days). At the cut-off date, 23% of patients had withdrawn from the study, with adverse events (9%), withdrawal of consent (8%), and lack of efficacy (4%) as the main reasons for treatment discontinuation. Average daily pain scores reduced from 6.3 at baseline, to 3.6 at the interim analysis (reduction of 2.7 points), with reductions sustained throughout the entire treatment period. Improvements from baseline in pain interference with sleep, pain interference with activity, and overall pain were 2.4, 2.3, and 3.1, respectively. Compared to baseline, QoL scores were reported to be increased after approximately 24 weeks of maintenance treatment in all eight domains of the SF-36, with pain related domains showing the largest increases [11]. However, no data are presented to assess the statistical or clinical significance of the differences reported.
Safety
In the fully published phase II study, 96 patients (81%) experienced at least one treatment-emergent adverse event (87% vs. 75% for the lacosamide and placebo groups, respectively) [10]. The most frequently reported events included headache (18% lacosamide vs. 22% placebo), dizziness (15% vs. 8%), nausea (12% vs. 7%), and diarrhoea (5% vs. 12%). Tachycardia, anxiety, and nervousness were all reported in 5% of lacosamide recipients vs. 0% for placebo. The majority of adverse events (AEs) were reported to be mild or moderate in intensity, with the first reports of most adverse events occurring in the titration phase. 53% of the adverse events in the lacosamide group and 36% in the placebo group were reported by investigators to be treatment related. Five lacosamide and three placebo recipients withdrew from the study within the first 19 days after randomisation due to an adverse event. Withdrawals from the lacosamide arm included two patients with liver enzyme elevations, one of which had high alkaline phosphatase levels at baseline and one in which liver enzymes reverted to normal within three weeks of stopping lacosamide. Overall, lacosamide showed no clinically important pattern in the minor QT/QTc increases.

Phase III safety data from the two double-blind, placebo controlled studies reported treatment emergent AEs in 60–82% of patients, and overall study discontinuation due to AEs occurred in 15–24% of patients [14,15]. The most common (incidence ≥5% in any lacosamide treatment group) treatment-emergent adverse events are summarised in Table 1.

The European phase III trial [14] did not identify any clinically relevant effects on ECG and laboratory parameters. Additionally, the use of a slower titration scheme was reported not to significantly affect the safety profile, although no details were provided. In the US trial, it was thought that blurred vision, nausea, dizziness, tremor, somnolence, and balance disorder may have been dose-related [15].

In the three open-label trials (including the two follow-on studies), treatment emergent AEs were experienced by 73–86% of patients. 22–30% of AEs were classed as mild, 40–43% as moderate, and 12–18% as severe in intensity [11–13]. The investigators in one of the follow-on studies (n=214) judged the majority (68%) of AEs as ‘unlikely to be related’ or ‘not related’ to trial medication. Of those side effects deemed to be related to lacosamide, nervous system effects were most common [12]. Those with an incidence of ≥5% in any of the studies included dizziness (12–20%), nausea (8–12%), vertigo (9–12%), headache (8–9%), somnolence (9%), and tremor (6%). 9–12% of patients withdrew due to AEs [11–13]. The most common side effects leading to discontinuation in one study were dizziness (2%), tremor (1%) and balance disorder (1%) [13]. There were no reports from any study of prolongation of the QTc interval or of clinically relevant effects on laboratory parameters. Data from two of the studies indicated that there was no trend in overall weight change with lacosamide treatment [11, 13].

Summary of Efficacy and Safety
Interpretation of the data from the placebo-controlled trials is difficult, as only one of these (phase II) has been published.

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<th>Table 1. Treatment-emergent adverse events (incidence ≥5% in any lacosamide group) in two phase III trials</th>
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<td>PLB</td>
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<tr>
<td>Discontinuation due to AEs</td>
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<tr>
<td>Any AE</td>
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<td>Dizziness</td>
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<td>Nausea</td>
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<td>Pruritus</td>
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PLB – placebo
LMD – lacosamide
in full [10], the definition of the primary endpoint appears to vary slightly between studies, and the results obtained are inconsistent. Statistical significance vs. placebo was reported to be reached in the phase II study [10]. It was also achieved at various weekly time points for the 400mg/day and 600mg/day doses explored in the US phase III study (secondary variables), but not for the primary endpoint of a reduction from baseline in daily pain scores in the last four weeks of the maintenance phase [15]. This pattern of results was also seen in the European phase III study [14].

More importantly, it needs to be ascertained if reductions in pain scores were clinically significant. On average, a reduction of approximately two points or 30% in an 11-point pain intensity numerical rating scale has been reported to represent a clinically important difference [16]. Across the placebo-controlled studies, lacosamide provided a reduction from baseline in the 11-point Likert pain scale at study end, of approximately 1.9 to 3.1 points, and it could be argued that these changes were clinically significant. However, a reduction of approximately 1.6 to 2.2 points occurred with placebo, and if the placebo response is removed then the magnitude of the reduction attributed to lacosamide would be approximately 0.3 to 0.9 points, which is below the threshold for clinical significance.

In terms of tolerability, discontinuation was high in the phase III trials, with one 18-week study reporting rates of 66% and 42% for lacosamide 600mg/day and 400mg/day, respectively, vs. 32% for placebo [15]. 42% of withdrawals from the 600mg/day arm were attributed to adverse events, with central nervous system (CNS) effects such as blurred vision, nausea, dizziness, tremor, somnolence, and balance disorder being possibly dose-related [15].

Open-label extension data suggests the effect of lacosamide is maintained over a prolonged period. However, these data must be viewed with caution as a large number of patients dropped out of the initial placebo-controlled trials. If results were obtained using only data for those patients still receiving lacosamide at the point of analysis, this may overestimate the effectiveness of lacosamide. Additional reasons for cautious interpretation of the results are the open-label and uncontrolled nature of the studies. It should also be noted that drop out rates were still relatively high in the two extension studies; 26% over a median duration of 358 days in one [12], and 30%, over a mean duration of 216 days in the other [13]. When viewed in context with the high drop out rates in the initial studies, long term adherence to lacosamide therapy could potentially be low.

As pain relief in PDPN is very seldom complete, measures of function, such as work and social activities, and quality of life, are important in assessing the response to treatment. Improvements in QoL have been reported in the phase II trial [10] and one of the phase III trials [14]. However, it is not possible to determine the clinical significance of the reported improvements due to a lack of data and detail. Other secondary measures used in the phase III controlled studies included the perception of pain interference with sleep and general activity but results are inconsistent; statistically significant differences over placebo were shown for these endpoints in one study [14], but not in the other [15].

The lack of relative efficacy data vs. existing therapies makes it difficult to determine where lacosamide fits into the treatment pathway of PDPN. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) implies that an intervention should reduce pain intensity from baseline by 30% to demonstrate adequate patient benefit. To permit comparisons with previous studies and meta-analyses, it is suggested that investigators should also report the percentages of patients obtaining reductions in pain intensity from baseline of at least 50% [17]. A recent systematic review of treatments for painful diabetic neuropathy used this criterion as the primary endpoint [6] and, whilst not a substitute for comparative studies, similar data for lacosamide would help in assessing its role in the treatment of PDPN. Additionally, more QoL data are required to help assess if changes in pain scores translate into physical and mental health benefits for patients.

### Treatment alternatives

There does not appear to be an international consensus on the preferred pharmacological treatments for PDPN although there are medicines licensed for use in neuropathic pain. It is recognised that off-label use of some agents ahead of these licensed medicines is often appropriate, as demonstrated by the current NICE clinical guideline for the treatment of type I diabetes [18]. This recommends initial treatment with simple analgesics (e.g. paracetamol) but if this is ineffective a low-to-medium dose TCA (unlicensed for this indication) is the next recommended step. If a TCA fails, a trial of gabapentin (up to the maximum tolerated dose or at least 1800mg per day) is recommended. If gabapentin fails, carbamazepine (unlicensed for this indication) and phenytoin (licensed for neuropathic pain treatment under specialist supervision) are alternative choices. If chronic pain continues, opiate analgesia and referral to pain management services should be considered. Where drug therapy is successful in alleviating symptoms, trials of reduced dosage and cessation of therapy should be considered after six months of treatment [18].

### Current drug usage

There are no national data on drug usage specifically in PDPN due to the broad indications (licensed and unlicensed) of the various agents that may be used.

### Estimated NHS impact

PDPN is a well documented condition with many established symptomatic treatment options. Whilst the efficacy of these treatments is far from ideal, no data are
available for lacosamide to suggest it offers an advantage over these existing therapies. As such, its introduction alone would not be expected to result in an increase in overall prescribing for PDPN. However, it is important to note that data suggest there are a significant proportion of patients with PDPN who have either not reported, or are not receiving treatment for their painful symptoms [4]. Additionally, as the incidence of diabetes is increasing, there will be more patients with the potential to develop complications such as PDPN [7].

As previously stated, there are no internationally approved consensus guidelines for the treatment of PDPN, but consensus-based recommendations have recently been made in the US [8]. These suggest that: first-line agents should be titrated to maximum tolerated doses and a reduction in pain of at least 50% from baseline should be expected if the agent is effective for that patient. Some improvement in pain levels should be expected within three weeks of initiating therapy. For patients not responding adequately to first-line treatment, or complaining of adverse events, a change should be made to another agent with a different mechanism of action. If necessary, add in a different agent using principles of rational polypharmacy (e.g. complementary mechanisms of action, avoid additive adverse events, consider possible synergies) [8].

The manufacturer anticipates that lacosamide will be used in patients either not responding to or not tolerating existing treatments, or where existing treatments are contraindicated. They have estimated that 4,318 patients may be treated with lacosamide for diabetic neuropathic pain in 2008, rising to 33,196 patients by 2011. Assuming an equivalent cost per patient per year to pregabalin, they estimate the cost to the NHS will be approximately £3.0 million in 2008, rising to over £27.0 million by 2011 [Personal Communication, UCB Pharma, July 2007]. Overall, if lacosamide is prescribed in place of pregabalin there should be no additional drug expenditure (assuming equivalent costs).

The Scottish Medicines Consortium (SMC) has rejected the use of pregabalin for peripheral neuropathic pain [19] and highlighted the paucity of evidence for the efficacy of pregabalin in patients who have already been treated with gabapentin ≥1200mg/day.

Many existing therapies are available as generics and the prescribing of a more expensive branded product in preference to these would lead to an increase in expenditure. Currently available efficacy and safety data for lacosamide do not support such a shift in prescribing. There is also the potential for lacosamide to be used ‘off-label’ for painful neuropathies other than those associated with diabetic peripheral neuropathy.

An application for marketing approval for lacosamide as an adjunctive therapy for epilepsy in adults was accepted by the EMEA in May 2007 [Personal Communication, UCB Pharma, August 2007].
Lacosamide

Points to consider in determining the place in therapy of lacosamide for the treatment of neuropathic pain associated with diabetic peripheral neuropathy

- There are many established symptomatic treatment options for PDPN, not all of which are licensed for this indication. The efficacy of these treatments is far from ideal, and data from clinical trials can be of poor quality due to small patient numbers and different outcome measures.

- The efficacy and safety of lacosamide in the treatment of PDPN has not been compared to existing treatments. Such data are required for lacosamide before its place in therapy can be fully assessed.

- Placebo-controlled studies have shown lacosamide reduces pain associated with PDPN. However, the clinical significance of the placebo-subtracted decreases in pain scores is unclear and not all results are consistent.

- Open-label studies have shown that the effect of lacosamide on pain reduction is maintained over a prolonged period, although the data need to be viewed with caution due to the potential for patient selection bias in the studies and the nature of their design.

- Drop-out rates from both short-term placebo-controlled studies, and longer term open-label studies were high (66% for lacosamide 600mg/day in one 18 week study [15]). Treatment-related adverse events predominantly affected the CNS (e.g. blurred vision, nausea, dizziness, tremor, somnolence, and balance disorder) and may be dose-related.

- Due to the modest effect of existing therapies on pain relief, measures of patient function (e.g. work and social activities) and quality of life are important in assessing response. Available data for these measures is limited.

- The prescribing of lacosamide in preference to established generic treatments for PDPN would increase drug expenditure. There are currently no data to support such a shift in prescribing. However, as treatment failure and subsequent switching of treatments is common in this clinical field, lacosamide may potentially provide an alternative to individuals who do not respond to existing treatments.

References